Self Study 3

HIV-Associated Lipodystrophy

***1. Define the terms lipodystrophy and lipoatrophy. How is ART-related lipodystrophy or lipoatrophy diagnosed? Is there is single definitive test?***

Lipodystrophy refers to both lipohypertrophy and lipoatrophy. Lipohypertrophy is the abnormal central fat accumulation, whereas lipoatrophy refers to the localized loss of fat tissue.

Lipohypertrophy in this syndrome is characterized by the presence of an enlarged dorsocervical fat pad, circumferential expansion of the neck, breast enlargement, and abdominal visceral fat accumulation.

Lipoatrophy is exemplified by peripheral fat wasting with loss of subcutaneous tissue in the face, arms, legs, and buttocks.

ART-related lipodystrophy is generally diagnosed through a physical exam. Measurements of the body are taken and then compared to a future physical exam to determine the change. There is no definitive test, but lipid assays and imaging can help determine fat accumulation/loss.

***2. What key metabolic changes in glucose and lipid metabolism might be expected in such patients (i.e. with ART-related lipodystrophy or lipoatrophy). Which of these might these patients share with obese individuals?***

In ART-related lipodystrophy, there tend to be problems with decreased insulin sensitivity and beta-islet cell dysfunction. This results in an elevated blood glucose level. There are also problems with lipoprotein receptor-related protein, which causes problems with the LDL receptor. This has a role in causing secondary hyperlipidemia that results from a failure of clearance of chylomicrons by the liver and tissues.

Similar symptoms would be seen in obesity. Obesity results in a decreased sensitivity of insulin receptors and ultimately leads to diabetes type II. Obesity will also likely include hyperlipidemia due to dietary cholesterol. LDL receptors will decrease in expression as the cells will have more than enough cholesterol, thus increasing the cholesterol in the blood.

***3. Describe the role of the below two classes of anti-retroviral therapy (ART) drugs in the clinical manifestation of HIV- associated lipodystrophy and lipoatrophy.***

***A.) Nucleoside analog reverse transcriptase inhibitors (NRTIs)***

***B.) Protease inhibitors (PIs)***

NRTIs inhibit mitochondrial DNA (mtDNA) polymerase gamma, leading to mtDNA depletion, respiratory chain dysfunction, and reduced energy production, which, in turn, causes insulin resistance and secondary dyslipidemia.

PIs have a high affinity for the catalytic site of HIV-1 protease, which shares a 60% sequence homology with 2 proteins involved in lipid metabolism, cytoplasmic retinoic acid–binding protein type 1 (CRABP-1), and low-density lipoprotein receptor–related protein (LDLR-RP). Some PIs, particularly ritonavir, inhibit cytochrome P450 3A, a key enzyme in lipid metabolism.

***4. How would patients with ART or HIV-related lipodystrophy or lipoatrophy be treated or managed? What is the mode of action of the drug Tesamorelin?***

Withdrawal of protease inhibitors will usually reverse the symptoms of lipodystrophy. Treatment of insulin resistance may include use of metformin, IGF-1, and DHEA. Treatment of the secondary hyperlipidemia may include fibrates and/or statins or DHEA by itself. Plastic surgery is also an option for treatment

Tesamorelin is a growth hormone–releasing factor analog. It acts on the pituitary gland and stimulates release of growth hormone. This, in turn, causes the breakdown of excess central fat.

***5. What type of abnormal cells/tissues comprise the “buffalo hump” found in HIV-infected patients on ART?***

The “buffalo hump” is essentially a fat pad that consists of adipocytes. The most common cause of buffalo hump is hormonal imbalance and excessive accumulation of fat. The hormonal imbalance is basically caused due to the elevated levels of cortisol released by adrenal glands. Buffalo Hump causes actually include medicinal side-effects of oral corticosteroid drugs such as prednisone, hydrocortisone, and certain AIDS medications.